REMARKS

Upon entry of this amendment, claims 1, 6, 7, 16-18, 26, 27, and 71-78 will be pending. New claims 74-78 are supported by the specification at, for example, Examples 2 and 3. Claims 1 and 18 have been amended. Claims 2-5, 8-15, 19-25, and 28-70 were previously canceled. No new matter is introduced by this amendment.

Applicants respectfully request reconsideration of allowance of the claims.

Claims 1, 6, 7, 12, 14-16, 18, 26, 27, and 71-73 comply with the written description requirement of 35 U.S.C. § 112, first paragraph.

Claims 1, 6, 7, 12, 14-16, 18, 26, 27, and 71-73 remain rejected under the first paragraph of 35 U.S.C. § 112 as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully disagree.

Compliance with the written description requirement of 35 U.S.C. § 112, first paragraph requires sufficient information in the original disclosure to convince an ordinarily skilled artisan that the inventor possessed the invention at the time of filing. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306 (Fed. Cir. 2003). The United States Patent and Trademark Office has determined that possession can be demonstrated by a disclosure of functional characteristics when coupled with a known or disclosed correlation between function and structure. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001).

The United States Court of Appeals for the Federal Circuit recently stated that written description requirement of section 112 for a genus by disclosure of a species can be satisfied if the operability in the invention of undisclosed species can be predicted based on the description of the properties and functions of the disclosed species. *In re Curtis*, 354 F.3d 1347, 1355-56, 69 U.S.P.Q.2D (BNA) 1274 (Fed. Cir. 2004).

Amended claim 1 and claim 72 encompass methods for making a hypermutable bacterium by introducing into a bacterium a polynucleotide encoding a dominant negative PMS2 mismatch repair protein that is a *truncated protein* (claim 1) or a dominant negative PMSR or PMS2L mismatch repair protein (claim 72) under the control of an inducible transcription regulatory sequence and inducing the inducible transcription regulatory sequence in the bacterium, such that the dominant negative mismatch repair protein exerts a

dominant negative effect on mismatch repair when expressed, thereby generating a hypermutable bacterium. Amended claim 18 and claim 73 are directed to homogeneous compositions of induced, cultured, hypermutable bacteria having a polynucleotide encoding a dominant negative PMS2 mismatch repair truncated protein (claim 18) or PMSR or PMS2L mismatch repair protein (claim 73) under the control of an inducible transcription regulatory sequence, wherein the dominant negative mismatch repair protein exerts a dominant negative effect when expressed.

The Patent Office asserts that the claims lack adequate written description because they recite a genus of PMS2, PMSR, or PMS2L mismatch repair proteins that can be expressed in any bacterium to exert a dominant negative effect on mismatch repair, *i.e.*, to produce hypermutable bacteria. Paper 20, page 3, lines 1-4. As evidence that the claims lack adequate written description the Patent Office cites Prudhomme *et al.* (*J. Bacteriol.* (1991) *173*:7196-7203) and Kondo *et al.* (*J. Biochem.* (1999) *125*:818-825). The Office Action alleges that Prudhomme and Kondo teach that although species of the genus of mismatch repair proteins is highly conserved, the proteins may not function as predicted. The Office Action asserts, "Notably, there are examples of highly conserved species of mismatch repair proteins that behave in an unexpected fashion." Paper 20, page 4, lines 19-20.

Prudhomme is cited as teaching that expression of a *Streptococcus pneumoniae* homologue of the *Escherichia coli* MutL protein, HexB, in *E. coli* does not increase the mutation rate of *E. coli*. The Office Action asserts that Prudhomme teaches that "even within bacterial species, it has been shown that expression of hexA, a *Streptococcus pneumoniae* homologue of *E. coli* MutS, causes hypermutability in *E. coli*, but significantly, expression of hexB, a homologue of MutL, does not." Paper 20, page 4, line 21 to page 5, line 1. Applicants respectfully assert that the Prudhomme reference has no bearing on the patentability of the present claims. HexB is neither a truncated dominant negative PMS2 mismatch repair protein, PMSR mismatch repair protein, nor PMS2L mismatch repair protein as required by the presently amended claims. Prudhomme, therefore, does not provide any reason to doubt that the claimed polynucleotides encoding a dominant negative truncated PMS2 protein, PMSR, or PMS2L protein will have a dominant negative effect on mismatch repair in bacteria.

Kondo is cited as teaching that "highly conserved species within the family of PMS2L proteins do not interact with a major DNA mismatch repair protein – hMLH." (paper 20, page 5, lines 4-6) and that "even highly conserved mismatch repair proteins may have

completely different roles in a cell, rather than involvement in mismatch repair mechanisms" (paper 20, page 5, lines 10-11). The Office Action concludes that "there is a level of unpredictability with respect to even highly conserved species of mismatch repair proteins" (paper 20, page 5, lines 8-9) and that therefore "it would logically follow that truncated versions of the same, i.e., at codon 134, would also not necessarily be involved in the prescribed function" (paper 20, page 5, lines 13-14). Kondo does not teach that the *PMS2L* genes encode mismatch repair proteins. In fact, Kondo teaches that the function of the proteins encoded by the *PMS2L* genes is unknown. Kondo teaches that "the total number of PMS2L genes in the human genome is unclear, as are the functions of their protein products." Page 822, column 2, lines 9-11. Because Kondo does not teach that the PMS2L proteins are mismatch repair proteins, Kondo does not support the assertion that it is unpredictable whether dominant negative PMS2L proteins will exert a dominant negative effect on mismatch repair across different bacterial species.

Furthermore, one of skill in the art would not have been surprised that the PMS2L proteins do not bind MLH1. The PMS2L proteins are structurally similar to PMS2-134. Kondo teaches, "The hPMS2-134 polypeptide contains the highly conserved amino-terminal domain of hPMS2 and structurally resembles PMS2Ls." Page 818, column 2, lines 12 to page 819, column 1, line 6. The PMS2-134 protein lacks the C-terminal amino acid residues of PMS2, which are the amino acid residues that interact with MLH1. "Herein we report that hMLH1 does not interact with PMS2Ls but does interact with the carboxyl terminal portion of hPMS2." Page 819, column 2, lines 6-8. In fact, Kondo teaches that a PMS2-261 protein, which has a greater number of C-terminal amino acid residues than PMS2-134, does not interact with hMLH1. "this immunoprecipitation study clearly demonstrated that hMLH1 forms protein complexes in vivo with hPMS2 and hPMS2(203-862) but shows no interaction with hPMS2(1-261), PMS2L13(1-179), or PMS2L16(9-83)." Page 824, column 2, lines 41-45. Thus, it would not have been surprising to one of skill in the art that proteins homologous to PMS2 but lacking its C-terminal amino acid residues, *e.g.*, PMS2-134 and PMS2L proteins, do not bind MLH1. If anything, one of skill in the art would expect the PMS2L proteins to function as dominant negative mismatch repair proteins because Kondo teaches that PMS2L proteins are structurally similar to PMS2-134 (see figure 2) and that, like PMS2-134, they do not bind MLH1.

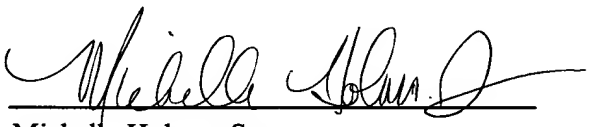
Kondo does not provide evidence that species of the genera of polynucleotides encoding a dominant negative PMS2 truncated protein or a dominant negative PMSR or PMS2L protein would not function in any bacteria to create hypermutability.

Applicants respectfully submit that their disclosure of several representative species of mismatch repair proteins of the claimed methods (see, for example, Examples 2 and 3 of the specification) establishes the requisite correlation between the art-recognized structural similarity of the claimed genus of dominant negative mismatch repair proteins and the dominant negative effect thereof on mismatch repair in bacteria. Withdrawal of the rejection is respectfully requested.

Abeyance of the provisional double patenting rejection is requested.

Claims 16, 17, and 71 are provisionally rejected for alleged obviousness-type double patenting over claims 1-3 and 36 of U.S Patent Application Serial No. 09/912,697 ("the '697 application"). Applicants note the provisional double patenting rejection and will address the rejection upon receipt of an indication that the claims are otherwise allowable. Abeyance of the rejection is respectfully requested.

Respectfully submitted,



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Michelle Holmes-Son
Registration No. 47,660

Customer No. 22907